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EXAMINER	
GODDARD, LAURA B	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 07/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/676,725	ROSENBLUM, MICHAEL G.	
	Examiner	Art Unit	
	Laura B. Goddard, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7,10,13,14,16,21 and 23-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7, 10, 13, 14, 16, 21, 23-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed May 3, 2006 in response to the Office Action of March 13, 2006, is acknowledged and has been entered. Claim 5 was canceled. Previously pending claims 7, 13, 21, 23, 24, 26, and 28 have been amended. New claims 30-31 have been added. Claims 7, 10, 13, 14, 16, 21, 23-32 are currently being examined.

Claim Objections

2. Claims 13, 14, 16, 21, 23, 24, and 25 are objected to because of the following informalities: Claim 24 depends on itself and claims 13, 14, 16, 21, 23, and 25 depend from claim 24. Appropriate correction is required.

NEW REJECTIONS

(necessitated by amendment)

NOTE: Applicant canceled base claim 5, of which claim 26 was dependent on. Given that Applicant did not amend claim 26 to bring the limitations of claim 5 into the claim, new base claim 5 raises new considerations and the Office Action is final.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 13, 14, 16, 21, 23, and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 24 recites the limitation "the protein with an antigen recognition site" and "the biological response modifier". There is insufficient antecedent basis for the limitations in the claims because claim 24 depends on itself.

NOTE: It appears Applicants intended to have claim 24 depend on claim 26. In the interest of compact prosecution, the claims will be examined as such.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 7, 10, 13, 14, 16, 21, and 23-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a WRITTEN DESCRIPTION rejection.

The claims are drawn to a method of treating cancer in a human patient in need of such treatment, the method comprising a) identifying a patient having a tumor, which

tumor comprises cells for targeting and wherein those cells comprise a **cell surface antigenic marker** at concentrations in excess of that found at other non-target sites; b) obtaining a composition comprising a **protein** with an antigen recognition site directed towards a cell surface associated antigen conjugated or fused to the biological response modifier, wherein it has been determined that cells of the patient's cancer express an antigen recognized and bound by **the protein** with an antigen recognition site; c) administering an amount of the composition to the patient effective to treat the cancer (claim 26), wherein the patient is diagnosed as having a tumor with a specific antigenic determinant that will allow targeting and concentration of the biological response modifier at the site where it is needed to kill tumor cells (claim 27), wherein the protein is an **antibody** (claim 28), wherein the antibody is a **monoclonal antibody** (claim 29), wherein the cancer is breast cancer, cervical carcinoma or melanoma (claims 7 and 30-32), wherein the protein with an antigen recognition site is conjugated or fused to the biological response modifier (claims 24 and 23, respectively), the method of claim 7 wherein the patient has been diagnosed with cancer and cells of the cancer express an antigen recognized by monoclonal antibody ZME-018 (ATCC accession number HB 11009) and further wherein the protein is a monoclonal antibody that recognizes and binds the antigen (claim 10), the method of claim 24 wherein the biological response modifier is a cytokine, TNF or TNF-alpha (claims 13, 14, and 16), the method of claim 24 wherein the protein's antigen recognition site recognizes and binds to the ZME-018 antigen, and antigen recognized by monoclonal antibody ZME-018 (ATCC accession number HB 11009) (claim 21).

The specification only discloses monoclonal antibody ZME-018 (ATCC accession number HB 11009) conjugated to TNF (ZME-TNF) used successfully in the treatment of melanoma that expresses ZME-018 antigen *in vivo* (Figure 10, Example 23). The specification discloses the breast cancer antigen 15A8 (p. 5) and monoclonal antibody 15A8, wherein MoAb15A8 conjugated to TNF can inhibit the growth of 15A8 antigen-positive cells in cell culture (Figure 6). The specification does not disclose any other cell surface antigenic markers or proteins and antibodies conjugated or fused to TNF as broadly encompassed in the claims.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a recitation of "cell surface antigenic marker at concentrations in excess of that found at other non-target sites", "protein with an antigen recognition site directed towards a cell surface associated antigen", "protein is an antibody", "wherein the antibody is a monoclonal antibody", "wherein the protein's antigen recognition site recognizes and binds to the ZME-018 antigen, and antigen recognized by monoclonal antibody ZME-018", "an antigen recognized by monoclonal antibody ZME-018". Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does

not provide adequate written description of the claimed genus of proteins, antibodies and cell surface antigenic markers.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that " [a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name', of the claimed subject matter sufficient to distinguish it from other materials. " Id. At 1567, 43 USPQ2d at 1405. The court also stated that:

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of proteins, antibodies and cell surface antigenic markers, per Lilly by structurally describing representative proteins, antibodies and cell surface antigenic markers or by

describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not directly describe proteins, antibodies and cell surface antigenic markers useful in the claimed invention in a manner that satisfies either the Lilly or Enzo standards. Although the specification discloses ZME-018 antibody (ATCC accession number HB 11009) which binds ZME-018 antigen and the 15A8 monoclonal antibody and antigen, this does not provide a description of the broadly claimed proteins, antibodies and cell surface antigenic markers that would satisfy the standard set out in Enzo because the specification provides no functional characteristics coupled to structural features.

Further, the specification also fails to describe proteins, antibodies and cell surface antigenic markers by the test set out in Lilly because the specification describes only ZME-018 antibody (ATCC accession number HB 11009) which binds ZME-018 antigen and the 15A8 monoclonal antibody and antigen. Therefore it necessarily fails to describe a representative number of such species.

Thus, the specification does not provide an adequate written description of proteins, antibodies and cell surface antigenic markers that is required to practice the

claimed invention. Since the specification fails to adequately describe the product to which the claimed method uses, it also fails to adequately describe the method.

Further, the following teaching of the court as set out in Noelle also clearly applies to the instant claimed invention. The court teaches as follows: "Noelle did not provide sufficient support for the claims to the human CD40CR antibody in his '480 application because Noelle failed to disclose the structural elements of human CD40CR antibody or antigen in his earlier '799 application. Noelle argues that because antibodies are defined by their binding affinity to antigens, not their physical structure, he sufficiently described human CD40CR antibody by stating that it binds to human CD40CR antigen. Noelle cites Enzo Biochem II for this proposition. This argument fails, however, because Noelle did not sufficiently describe the human CD40CR antigen at the time of the filing of the '799 patent application. In fact, Noelle only described the mouse antigen when he claimed the mouse, human, and genus forms of CD40CR antibodies by citing to the ATCC number of the hybridoma secreting the mouse CD40CR antibody. If Noelle had sufficiently described the human form of CD40CR antigen, he could have claimed its antibody by simply stating its binding affinity for the "fully characterized" antigen. Noelle did not describe human CD40CR antigen. Therefore, Noelle attempted to define an unknown by its binding affinity to another unknown. As a result, Noelle's claims to human forms of CD40CR antibody found in his '480 application cannot gain the benefit of the earlier filing date of his '799 patent application. Moreover, Noelle cannot claim the genus form of CD40CR antibody by

simply describing mouse CD40CR antigen". *Randolph J. Noelle v Seth Lederman, Leonard Chess and Michael J. Yellin* (CAFC, 02-1187, 1/20/2004).

In the instant application, the specification only discloses the monoclonal antibodies ZME-018 and 15A8. The instant application does not however fully describe the ZME-018 antigen nor the 15A8 antigen.

Since the instant application does not fully describe the genus of antigen to which the claimed protein or antibody or monoclonal antibody binds, the instant application cannot claim the genus form of protein or antibody or monoclonal antibody by simply describing monoclonal antibody ZME-018 or monoclonal antibody 15A8. Thus the specification fails to describe the claimed protein or antibody or monoclonal antibody, by the test set out in the example of Noelle.

5. Claims 7, 10, 13, 14, 16, 21, 23-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for **a method of treating melanoma in a human patient comprising the steps of: a) identifying a patient having a tumor that expresses the ZME-018 antigen; and b) administering monoclonal antibody ZME-018 (ATCC accession number HB 11009) conjugated or fused to TNF in an amount effective to treat the cancer**, does not reasonably provide enablement for a method of treating cancer in a human patient in need of such treatment, the method comprising a) identifying a patient having a tumor, which tumor

comprises cells for targeting and wherein those cells comprise a cell surface antigenic marker at concentrations in excess of that found at other non-target sites; b) obtaining a composition comprising a protein with an antigen recognition site directed towards a cell surface associated antigen conjugated or fused to the biological response modifier, wherein it has been determines that cells of the patient's cancer express an antigen recognized and bound by the protein with an antigen recognition site; c) administering an amount of the composition to the patient effective to treat the cancer, wherein the cancer is breast, cervical or melanoma. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the

presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method of treating cancer in a human patient in need of such treatment, the method comprising a) identifying a patient having a tumor, which tumor comprises cells for targeting and wherein those cells comprise a cell surface antigenic marker at concentrations in excess of that found at other non-target sites; b) obtaining a composition comprising a protein with an antigen recognition site directed towards a cell surface associated antigen conjugated or fused to the biological response modifier, wherein it has been determines that cells of the patient's cancer express an antigen recognized and bound by the protein with an antigen recognition site; c) administering an amount of the composition to the patient effective to treat the cancer (claim 26), wherein the patient is diagnosed as having a tumor with a specific antigenic determinant that will allow targeting and concentration of the biological response modifier at the site where it is needed to kill tumor cells (claim 27), wherein the protein is an antibody (claim 28), wherein the antibody is a monoclonal antibody (claim 29), wherein the cancer is breast cancer, cervical carcinoma or melanoma (claims 7 and 30-32), wherein the protein with an antigen recognition site is conjugated or fused to the biological response modifier (claims 24 and 23, respectively), the method of claim 7 wherein the patient has been diagnosed with cancer and cells of the cancer express an antigen recognized by monoclonal antibody ZME-018 (ATCC accession number HB 11009) and further wherein the protein is a monoclonal antibody that recognizes and

binds the antigen (claim 10), the method of claim 24 wherein the biological response modifier is a cytokine, TNF or TNF-alpha (claims 13, 14, and 16), the method of claim 24 wherein the protein's antigen recognition site recognizes and binds to the ZME-018 antigen, and antigen recognized by monoclonal antibody ZME-018 (ATCC accession number HB 11009) (claim 21). The claims are broadly drawn to treating **any cancer** in a patient, wherein the patient has a tumor cells comprising **any cell surface antigenic marker,** comprising administering **any protein, antibody or monoclonal antibody** that binds to the cell surface antigenic marker, conjugated or fused to **any biological response modifier.**

The specification discloses the *in vivo* treatment of melanoma tumors in mice comprising administering monoclonal antibody ZME-018 (ATCC accession number HB 11009) conjugated to TNF (ZME-TNF) (Figure 10, Example 23). The specification discloses the localization of ZME-TNF to melanoma tumor (Figure 9). The specification also discloses monoclonal antibody 15A8 (MoAb15A8) conjugated to TNF which binds to antigen 15A8 expressed by breast cancer cells and inhibits cell growth *in vitro* (Figure 6). The specification discloses a non-limiting example of biological response modifier wherein "biological response modifiers such as TNF may be obtained from sera of intact animals, culture supernatants of lymph cells or cell lines after the animals or cells had been treated with a substance known to stimulate the proliferation of immune cells (an inducer) or by recombinant technology" (p. 13).

One cannot extrapolate the teaching of the specification to the scope of the claims because the specification does not provide guidance or examples for treating

any cancer with **any protein or antibody** conjugated or fused to **any biological response modifier**, other than treating melanoma that expresses ZME-018 antigen comprising administering ZME-TNF. The specification discloses that breast tumor cells express an antigen 15A8 (p. 5), however, the specification does not provide examples or guidance for treating breast cancer comprising administering monoclonal antibody 15A8 conjugated to a biological response modifier. The specification also does not provide guidance or examples for treating cervical cancer with a protein conjugated to a biological response modifier.

With regards to the *in vitro* inhibition of breast cancer cell growth comprising administering MoAb15A8, those of skill in the art recognize that *in vitro* assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Hence, the *in vitro* example for MoAb15A8 conjugated to TNF inhibiting cell growth in cell culture as provided by the specification does not enable the claimed invention for *in vivo* treatment of cancer.

The art teaches that monoclonal antibody ZME-018 binds ZME-018 antigen expressed in melanoma tumors of patients. Kirkwood et al (J of clinical Oncology, 1987,

5:1247-1255) teach that monoclonal antibody ZME-018 specifically recognizes a melanoma-associated antigen of 240,000 molecular weight (gp240) wherein the antigen has exhibited greater restriction to melanoma than other antigens (p. 1247). Krizan et al (Cancer Research, 1985, 45:4904-4909) teach that ZME-018 is one of several monoclonal antibodies reactive with individual cell surface melanoma-associated antigens from tumor biopsies and that radioimmunoassay with individual monoclonal antibodies or cocktails of different antibodies revealed the heterogeneity of melanoma tumors in the antigens that they express (abstract, p. 4904; p. 4908, col. 2). A review of the prior and current art teach the expression of ZME-018 antigen in melanoma and not in other cancers. Clearly, ZME-018 antigen is a melanoma-associated antigen and is not associated with other cancers such as breast or cervical, hence only melanoma could be treated comprising administering ZME-TNF to a patient who has cancer that expresses ZME-018 antigen. Krizen et al teach that there are several antigens associated with melanoma and several monoclonal antibodies that recognize and specifically bind to them, indicating antigens other than ZME-018 are expressed in melanoma. Given the disclosure of the specification and teachings in the art, one of skill in the art could not predictably treat any cancer comprising administering an effective amount of any protein or any antibody conjugated or fused to a biological response modifier, other than treating melanoma that expresses ZME-018 antigen comprising administering ZME-TNF.

Therefore, in view of the state of the art, the breadth of the claims, lack of guidance in the specification, and the absence of working examples, it would require

undue experimentation for one skilled in the art to practice the invention as broadly claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 7, 26-29, and 32 rejected under 35 U.S.C. 103(a) as being unpatentable over Oldham et al (Cancer, 1984, 54:2795-2806) in view of Freeman et al (Cancer, 1986, 67:1680-7).

The claims are drawn to a method of treating cancer in a human patient in need of such treatment, the method comprising a) identifying a patient having a tumor, which tumor comprises cells for targeting and wherein those cells comprise a cell surface antigenic marker at concentrations in excess of that found at other non-target sites; b) obtaining a composition comprising a protein with an antigen recognition site directed towards a cell surface associated antigen conjugated or fused to the biological response modifier, wherein it has been determines that cells of the patient's cancer express an antigen recognized and bound by the protein with an antigen recognition site; c) administering an amount of the composition to the patient effective to treat the cancer (claim 26), wherein the patient is diagnosed as having a tumor with a specific antigenic

determinant that will allow targeting and concentration of the biological response modifier at the site where it is needed to kill tumor cells (claim 27), wherein the protein is an antibody (claim 28), wherein the antibody is a monoclonal antibody (claim 29), wherein the cancer is melanoma (claims 32 and 7), wherein the protein with an antigen recognition site is conjugated to the biological response modifier (claim 24).

Oldham et al teach the monoclonal antibody 9.2.27 which recognizes an antigen expressed on melanoma cells and localizes to tumor cells, hence the recognized antigen is a cell surface antigenic marker that is expressed in excess on melanoma cells as compared to normal tissue. Patients were identified as having tumors that reacted with antibody 9.2.27 *in vitro* and were treated with antibody 9.2.27, resulting in a decrease in melanoma skin lesions, lymph nodes or visceral metastasis (p. 2802, col. 2; p. 2804, col. 2). Oldham et al teach the use of biological response modifiers for cancer treatment (p. 2805, col. 1; p. 2806, col. 1). Oldham et al teach that the selective localization of the monoclonal antibody on the tumor-cell membrane suggests that these agents may be useful in specific targeting of cancer therapy, wherein monoclonal antibodies can be used to carry drugs, toxins and radioisotopes to the cancer cell with specificity (p. 2805 col. 2 through p. 2806, col. 1). Oldham et al does not teach treating cancer comprising administering the monoclonal antibody conjugated to a biological response modifier.

Freeman et al teach the use of monoclonal antibodies in cancer therapy by conjugating them to a biological response modifier, and that monoclonal antibodies serve to selectively transport agents to target cells without delivery to non-target cells

(p. 578, col. 2). Targeted drug delivery would simultaneously increase tumor kill and decrease toxicity (p. 581, col. 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to treat cancer in a human patient comprising administering the antibody taught by Oldham et al conjugated to a biological response modifier taught by Freeman et al in the method of Oldham et al because both references teach the use of monoclonal antibodies to target drugs for cancer treatment. One would have been motivated to administer the monoclonal antibody conjugated to a biological response modifier in the method taught by Oldham et al in order to simultaneously increase tumor kill and decrease toxicity by selectively targeting the biological response modifier to the melanoma cancer, hence treating the cancer.

7. Claims 13, 14, and 16, are rejected under 35 U.S.C. 103(a) as being unpatentable over Oldham et al (Cancer, 1984, 54:2795-2806) and Freeman et al (Cancer, 1986, 67:1680-7) in view of Ferris et al (US Patent 4,771,128, issued 9/13/1988, filed 10/10/1986) and Bregman et al (J Biol Response Mod, 1988, 7:384-389).

The claims are drawn to the method of claim 24 wherein the biological response modifier is a cytokine (claim 13), the method of claim 13, wherein the cytokine is TNF (Claim 14), the method of claim 14, wherein the TNF is TNF-alpha (claim 16).

Oldham et al and Freeman et al teach a method of treating cancer comprising administering an antibody conjugated to a biological response modifier as set forth

above. The combined references do not teach that the biological response modifier is the cytokine TNF or TNF-alpha.

Ferris et al teach immunoconjugates comprising a monoclonal antibody and TNF, wherein the monoclonal antibodies bind selectively to receptors found on target cells and TNF is a cytotoxic cytokine. (col. 2, lines 61-62; col. 3, lines 5-16; Examples 1-3).

Bregman et al teach that TNF-alpha can kill human melanoma cells (abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer a monoclonal antibody conjugated to TNF-alpha in the method taught by Oldham et al and Freeman et al because Ferris et al teach the conjugation of monoclonal antibodies to TNF and Bregman et al teach that TNF-alpha kills human melanoma cells. One would have been motivated to administer the monoclonal antibody conjugated to TNF-alpha in order to selectively target the TNF-alpha to melanoma cells that express the antigen that the monoclonal antibody recognizes, hence killing the melanoma cells and treating the cancer.

8. Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Oldham et al (Cancer, 1984, 54:2795-2806) and Freeman et al (Cancer, 1986, 67:1680-7) in view of US Patent 5,135,736, Anderson et al, filed 8/15/1988.

The claim is drawn to the method of claim 24 wherein the protein with an antigen recognition site is fused to the biological response modifier (claim 23).

Oldham et al and Freeman et al teach a method of treating cancer comprising administering an antibody conjugated to a biological response modifier as set forth

above. The combined references do not teach that the antibody is fused to the biological response modifier.

US Patent 5,135,736 teaches the manufacture of fusion proteins comprising an antibody and a cytotoxic agent wherein the fusion protein is produced through recombinant DNA technology (col. 2, lines 16-30; col. 12, lines 55-61; Example IV). US Patent 5,135,736 teaches method for enhancing *in vivo* cytotoxicity of a targeting protein conjugate comprising administering the conjugated protein or antibody to a tumor-bearing patient and a method for enhanced *in vivo* imaging of a tumor comprising administering the same conjugated protein or antibody (col. 1, lines 55-64). US Patent 5,135,736 teaches that the formation of a covalently-linked complex, such as an antibody-cytotoxic agent fusion protein, allows increased retention of the targeted protein or antibody conjugate at the plasma membrane of a target cell (col. 14, lines 26-31).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use a fusion protein as taught by US Patent 5,135,736 in the method of treating cancer taught by the combined references because US Patent 5,135,736 teaches the recombinant production of an antibody fused to a cytotoxic agent. One would have been motivated to use a fusion protein comprising an antibody used to a cytotoxic agent, such as a biological response modifier, in the method taught by the combined references because US Patent 5,135,736 teaches that an antibody fused to a cytotoxic agent increases retention of the targeted protein or antibody

conjugate at the plasma membrane of a target cell, hence enhancing *in vivo* cytotoxicity of the targeting fusion protein to treat the targeted cancer.

9. **Conclusion:** No claim is allowed. Claims 10, 21, and 24, 25, 30, and 31 are rejected under 35 U.S.C. 112, first paragraph but appear to be free of the prior art. The closes prior art appears to be Krizan et al (Cancer Research, 1985, 45:4904-4909). Krizan et al teach the detection of ZME-018 antigen in melanoma tumor biopsies using monoclonal antibody ZME-018 conjugated to a radiolabel. Krazen et al does not teach or suggest a method of treating melanoma or cancer comprising administering ZME-TNF or any protein or antibody conjugated or fused to TNF.

10. All other rejections in the Office Action mailed March 13, 2006 are withdrawn.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. ' 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. ' 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard, Ph.D. whose telephone number is (571) 272-8788. The examiner can normally be reached on 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura B Goddard, Ph.D.
Examiner
Art Unit 1642

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER